

## **REMARKS**

### **Claim Amendments**

Claim 1 is amended to recite human populations. The specification supports this amendment, for example, within the title of the application: “Allelic Variation In Human Gene Expression.”

Claim 1 is also amended to recite “wherein expression of the allele is determined independent of the expression of other alleles of the gene.” This limitation was originally presented within originally filed claim 8, which is now canceled.

The last step of claim 1 is amended for clarity to correspond better with the preceding steps of the claim. Also, claim 1 is amended to recite that the affected and control individuals are heterozygous for the gene, as recited in originally filed claims 5 and 6. These amendments place the claim in a better form.

Claims 5 and 6 are canceled.

Claim 19 and 32 are amended to recite that the first and second alleles are of the non-imprinted gene. This amendment places the claims in a better form.

Claim 32 is also amended to include a comparison step, as recited within originally filed claim 33. Claim 33 is canceled.

No new matter is added.

### **Informalities**

Claims 32 and 33 are noted as informal. This paper amends claim 32 by including a comparison step. The comparison step for claim 32 was accidentally written

as separate claim 33 in the original filing. Claim 33 is canceled and its subject matter is included within claim 32. Amended claim 32 is complete and proper.

Rejection of Claims 34 and 33 under 35 U.S.C. §112, 2<sup>nd</sup> Paragraph

Claims 34 and 33 are rejected under 35 U.S.C. §112, 2<sup>nd</sup> Paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Applicants respectfully traverse the rejection.

Claim 34 is clear and definite. No indefiniteness has been specifically indicated by the rejection.

In view of the noted informalities in original claims 32 and 33, Applicant assumes that the Office Action's rejection of claims 34 and 33 under 35 U.S.C. §112 is a typographical error and that the rejection should have been directed to claims 32 and 33. As described above, claim 32 is amended to recite a comparison step and claim 33 is canceled. Amended claim 32 is clear and definite.

Please withdraw the rejection.

Rejection of claims under 35 U.S.C. §102 (b)

Claims 1-6, 9-16, and 34-35 stand rejected under 35 U.S.C. §102 (b) as being anticipated by Lapidus et al. U.S. Patent No. 5,928,870 ("the '870 patent"). Applicants respectfully traverse the rejection.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal*

*Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is contained in the claimed invention. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989).

Independent claims 1, 34, and 35 recite, *inter alia*, methods of measuring allelic expression comprising determining levels of expression of an allele of a gene. As indicated in each of the claims, gene expression is determined. Gene expression relates to an expression product such as mRNA or protein. This is distinct from gene copy number which refers to DNA.

The '870 patent does not teach determining levels of gene expression. The '870 patent teaches, a "method for counting (*i.e.* enumerating) the number of molecules of a target genomic sequence present in a sample." See column 2, lines 58-60. The '870 patent teaches determination of gene copy number, not gene expression. The former can be used to detect, for example, loss of heterozygosity and quantifies the amount of a particular DNA sequence. The latter is a measure of mRNA transcribed or protein translated from a particular gene. These are fundamentally different measurements. The '870 patent does not teach measurement of expression products and thus does not teach each and every element of claims 1-6, 9-16, and 34-35. The '870 patent does not, therefore, anticipate the claims.

Rejection of claims 1-15, 17, 19-20 and 22-33.

Claims 1-15, 17, 19-20, and 22-33 stand rejected under 35 U.S.C. §102 (b) as being anticipated by Lapidus et al. U.S. Patent No. 6,146,828, ("the '828 patent"). Applicants respectfully traverse.

Re: Claims 1-15 and 17

Amended independent claim 1, the only independent claim of the group of claims 1-15 and 17, recites determining levels of expression of an allele of a gene in first and second populations, wherein expression of the allele is determined independently of the expression of other alleles of the gene, comparing the levels of expression of the allele of the gene in both populations, and identifying the allele of the gene as having an association with a phenotype if the levels differ in a statistically significant manner between the first and the second populations.

The ‘828 patent provides an example which teaches, “the ratio of p53 mRNA to beta-globin mRNA is determined in both the patient sample and the reference sample.” In this example, the expression of both the maternal and paternal alleles of the p53 gene are inherently included in the measured expression level. The p53 expression level encompasses the gross expression level of both alleles. Nowhere does the ‘828 patent teach determining levels of expression of a p53 or beta-globin allele, wherein the expression of the allele is determined independently of the expression of other alleles of the gene, as recited by claim 1.

The ‘828 patent also teaches “determining a ratio of RNA expressed by a paternal allele to RNA expressed by a maternal allele.” See column 3, lines 2-3. This embodiment involves the creation of a ratio of expression between two discrete alleles of one gene within one individual. Amended claim 1 recites determining levels of expression of one allele of a gene in two different populations of individuals (“determining levels of expression of an allele of a gene in a first human population” and “determining levels of expression of the allele of the gene in a second population”). This

is not taught by the ‘828 patent. Thus, the ‘828 reference does not anticipate claims 1-15 and 17 because the reference does not teach each and every element of claim 1 and therefore also does not anticipate dependent claims 2-15 and 17.

Re: Claims 19-20 and 22-32

Independent claims 19 and 32, the only independent claims of claims 19-20 and 22-32, recite, *inter alia*, methods of measuring allelic expression variation comprising reverse transcribing and amplifying mRNA from an individual heterozygous for a single nucleotide polymorphism (SNP) in a non-imprinted gene to form a first cDNA from a first allele and a second cDNA from a second allele. Nowhere does the ‘828 patent teach reverse transcribing and amplifying mRNA of a non-imprinted gene from an individual heterozygous for a single nucleotide polymorphism in the non-imprinted gene. At most, the ‘828 patent teaches detecting “maternal or paternal imprinting, wherein disease results from reduced expression or non-expression of either the maternal or paternal allele.” See column 3, at lines 46-49. There is no teaching of reverse transcribing and amplifying mRNA from an individual heterozygous for a single nucleotide polymorphism in a non-imprinted gene. Thus, the ‘828 patent does not teach each and every element of claims 19-20 and 22-32.

Applicants respectfully request withdrawal of the rejection.

Rejection of Claims 18 and 21 Under 35 U.S.C. §103

Claims 18 and 21 are rejected under 35 U.S.C. §103 as being obvious over Lapidus et al. (“the ‘828 patent”) in view of Lapidus et al. (“the ‘870 patent”). Applicants respectfully traverse the rejection.

The U.S. Patent and Trademark Office bears the initial burden of establishing a *prima facie* case of obviousness. The *prima facie* case requires three showings:

First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Manual of Patent Examining Procedure, 8<sup>th</sup> ed., § 2142. The Patent Office has not made a *prima facie* case of obviousness because the prior art references, when combined, do not teach or suggest all the claim limitations.

Claims 18 and 21 are dependent on claims 1 and 19, respectively. As discussed above, the ‘870 patent teaches gene copy number, a fundamentally different measurement than gene expression, which is recited by claims 1 and 19. Also, as discussed above, the ‘828 patent teaches the creation of a ratio between two discrete alleles of the p53 gene within one individual. Claim 1 recites determining levels of expression of one allele in two different populations of individuals. This is a completely different measurement than what is taught by the ‘828 patent. The ‘828 patent also teaches detecting imprinting, wherein disease results from reduced expression or non-expression of an allele. Claim 19 recites reverse transcribing and amplifying mRNA of a non-imprinted gene from an individual heterozygous for a single nucleotide polymorphism. Again, this is a completely different measurement. The cited references do not teach or suggest any of

the limitations of independent claims 1 and 19. For at least this reason, the obviousness rejection of dependent claims 18 and 21 should be withdrawn.

Moreover, claims 18 and 21 recite determining and/or comparing expression levels using capillary electrophoresis. The Office Action points to column 5, lines 9-21 of the '870 to support the obviousness rejection, however this passage only refers generally to separating oligonucleotides by gel electrophoresis, chromatography, or mass spectrometry. Nowhere within the '870 patent is there a teaching or suggestion of using capillary electrophoresis. The cited references, when combined, do not teach or suggest all of the claim limitations of claims 18 and 21. Thus, claims 18 and 21 are not obvious over the cited references.

Applicants respectfully request withdrawal of the rejection.

Respectfully submitted,

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